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### **Cholinesterase inhibitors should not be prescribed for mild cognitive impairment**

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**Category:** Therapeutics

**Study type:** Systematic review and meta-analysis

**Author's declarative title:** Cholinesterase inhibitors should not be prescribed for mild cognitive impairment

**Citation:** Tricco AC, Soobiah C, Berliner S, et al. Efficacy and safety of cognitive enhancers for patients with mild cognitive impairment: a systematic review and meta-analysis. *CMAJ* 2013; **185**: 1393-1401.

### **Context**

Dementia is a chronic disease with insidious onset. Thus, Alzheimer disease can be present years, or even decades, before the clinical onset of Alzheimer dementia.<sup>1,2</sup> Much research attention is being paid to biomarkers which, singly or in combination, may help identify which patients will go on to develop Alzheimer dementia while they are still asymptomatic, but their predictive validity is still inadequate.<sup>3</sup> Many patients seen in clinical practice fall into the grey area of having some, relatively minor, memory problems which have little impact on their day-to-day functioning. These criteria are at the core of all definitions of mild cognitive impairment (MCI) and similar categories, the prognosis of which are difficult to forecast. The cognitive component can be more accurately characterised with a longitudinal assessment. However, the question of whether or not a patient's functional ability is 'normal' is, in fact, a value judgement related to expectation. Values are integral to all medical diagnoses, although they are not always explicitly apparent.<sup>4</sup> With clear benefits ensuing from appropriate early diagnosis, the question of how early a person can be diagnosed with dementia is not mere academic speculation. It has clear clinical relevance regarding the starting of memory treatment and it is vital to acknowledge the value judgement at the centre of this question. There is evidence from several systematic reviews that cholinesterase inhibitors are not efficacious in MCI and are associated with substantial side effects.<sup>5-7</sup>

### **Methods**

This review included experimental, quasi-experimental or observational studies of memory treatment (cholinesterase inhibitors or memantine) in people with MCI. The outcomes reported were: change in cognition (measured by the Mini-Mental State Examination and the Alzheimer disease assessment scale cognitive subscale), function (measured by the Alzheimer Disease Cooperative Study Inventory-Activities of Daily Living), behaviour (measured by the NPI), mortality and side effects. The protocol was registered in advance of the study and the authors followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines in their reporting of the review. Results are reported as relative risks (RR) and CI.

### **Findings**

Eight RCTs (reported in 10 papers) including 4711 people with MCI were included in the review. Only one study investigated the use of memantine for MCI and this was only included in the serious adverse events analysis. There were no differences seen in terms of cognition, function or behaviour between individuals receiving cholinesterase inhibitors or placebo. Similarly, there was no difference in mortality—overall or treatment-related—or serious adverse events between the cognitive enhancer and placebo groups. However, substantially higher nausea (RR=3.04, 95% CI 2.52 to 3.66), diarrhoea (RR=2.33, 95% CI 1.74 to 3.13), vomiting (RR=4.40, 95% CI 3.21 to 6.03) and

headaches (RR=1.27, 95% CI 1.04 to 1.53) were reported in the treatment groups compared with placebo. Similar results were seen in the single study reporting treatment-related harms. A single study of galantamine reported more bradycardia (RR=1.52, 1.04 to 2.22), but fewer falls (RR=0.71, 95% CI 0.52 to 0.98) compared with placebo.

### **Commentary**

This systematic review and meta-analysis is the first to differentiate between overall harms and treatment-related harms. Nevertheless, its findings echo those of a series of earlier systematic reviews.<sup>5-7</sup> This is the first review to include memantine but only one study examined this drug and it could only be included in a subset of analyses. Presumably because of the limited number of studies, the authors combined outcomes from a wide variety of study durations and performed meta-regression to investigate different effects over time.

It is concerning that the authors report these medications can be obtained by special authorisation in Canada, as the evidence is clear — cholinesterase inhibitors and memantine should not be prescribed in MCI. However, the core problem is a philosophical one: MCI is a description, not a diagnosis and further research attention is urgently required to better characterise people with minor cognitive impairment and minimal functional impairment in order to be able to predict who will go on to develop clinical dementia and who will not.

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### **Competing interests**

None